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EDITOR'S PAGE

# Neoatherosclerosis: Fooling Mother Nature

**Spencer B. King III, MD, MACC**

Editor-in-Chief, *JACC: Cardiovascular Interventions*

Thirty-seven years ago, I stood in front of Andreas Gruentzig's poster at the American Heart Association's Scientific Session wondering how balloon inflation in a coronary artery would lead to anything good. I told him that it would never work, and I was wrong. However, the coronary artery did not quietly capitulate to this rude disruption, but fought back with a healing process that kept undoing the work of the balloon. The evolution of percutaneous coronary intervention has provided a laboratory for vascular biology research. With every advance in coronary intervention, we have produced new problems, which require new solutions, which produce new problems. Does the cycle ever end? Perhaps not, although the struggle has clearly been worth it, as millions of patients can testify. But, are we finished?

A balloon opens the obstruction and removes the pressure gradient that was producing ischemia; however, the elasticity of the artery and the exposure of thrombogenic substrate frequently lead to acute vessel closure. If not, the cytokines release and the "scar" retraction that follows leads to restenosis. Stents were the mechanical solution to the mechanical problem, but Mother Nature did not remain fooled for long; the exuberant healing response, driven in part by the chronic stretch stimulus, resulted in in-stent restenosis. Briefly, we dreamed that controlling the components of thrombosis would prove a solution, but it did not. The cell migration and proliferation seen in restenosis are common mechanisms in cancer and wound healing. So, we tried radiation, which was shown to have been variously effective in both of those conditions. The growth of neointima was effectively blocked by radiation brachytherapy, but so was the formation of well-functioning endothelium. Knowledge of the effectiveness of blocking the cell cycle led to the inevitable combining of the structural solution of the mechanical problem (stents) with drugs that suppressed the exuberant healing response (drug-eluting stents). Drug-eluting stents are where we are now, but has Mother Nature been completely fooled this time? The components of drug-eluting stents (the scaffold, the polymer, and the drug) have each been implicated in late stent failure that has not been completely eliminated. New systems are being developed to change the drug, change or eliminate the polymer, or remove the metal scaffold completely (bioresorbable stents). Has percutaneous coronary intervention finally triumphed over Mother Nature?

After the time for acute closure and restenosis has passed, and the stent is well covered with new tissue, are we "off the hook?" Perhaps not. The new problem that is receiving substantial attention is in-stent neoatherosclerosis and its potential risk for patients who largely forgot about their stents years ago. It is not clear what produces this phenomenon, but histologically, it is made up of lipid-rich core, macrophage infiltration, and sometimes, a thin-cap fibroatheroma. Neovascularity and intraplaque hemorrhage have been observed. In short, it looks like atherosclerosis of the usual variety, but perhaps more aggressive. In vivo diagnosis is now also possible, with optical coherence tomography and near-infrared spectroscopy showing, respectively, the thin-cap fibroatheroma and the lipid core. Why does this occur in some patients years after apparent healing of the stented segment and adequate coverage of the stent struts with neointima? The polymer delivery system has been implicated in producing an inflammatory response leading to atheromatous changes. The drugs used to inhibit cell growth have also been implicated. Scanning electron microscopically-generated images of the endothelial surface show disordered cells with abnormal gap junctions instead of the well-ordered cobblestone appearance of normally functioning endothelium. These changes are reminiscent of those seen after radiation brachytherapy. Could such altered endothelium be more permeable to macrophage infiltration and subsequent atherosclerosis?

What is the magnitude of the problem? There are more reports of neoatherosclerotic complications with first-generation stents than with the stents now commonly used. Is this only because the time passed is greater with first-generation stents? Hopefully, improved stents will heal with

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fewer stimuli for the phenomenon to occur, but there are millions of first-generation stents in our patients' coronary arteries now. What should the interventional approach be to obstructive in-stent restenotic lesions that may have neoatherosclerosis? Should very late restenosis be investigated with optical coherence tomography? Should interventional approaches be altered if lipid-rich core and thin-cap fibroatheroma are observed? Should aggressive antithrombotic or distal embolic measures be employed? Will aggressive medical therapy stabilize or reduce the progression of neoatherosclerosis? Will the disappearance of the bioresorbable stent eliminate neoatherosclerosis?

Fortunately, most of our patients are doing fine, or if not, the problem they face most likely arises from parts of the coronary tree not previously stented rather than from the stented segment. Nonetheless, the occasional development of in-stent neoatherosclerosis after we thought we were out of the woods once again proves that fooling Mother Nature remains a work in progress.

**Address correspondence to:**
Spencer B. King III, MD, MACC
Saint Joseph's Heart and Vascular Institute
5665 Peachtree Dunwoody Road NE
Atlanta, Georgia 30342
spencer.king@emoryhealthcare.org